

PATENT COOPERATION TREATY

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)

Date of mailing
(day/month/year) 05.03.2001

Applicant's or agent's file reference
TSJ/TC/34953

IMPORTANT NOTIFICATION

International application No.
PCT/IB99/02018

International filing date (day/month/year)
26/11/1999

Priority date (day/month/year)
27/11/1998

Applicant
LUDWIG INSTITUTE FOR CANCER RESEARCH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference TSJ/TC/34953		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB99/02018	International filing date (<i>day/month/year</i>) 26/11/1999	Priority date (<i>day/month/year</i>) 27/11/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant LUDWIG INSTITUTE FOR CANCER RESEARCH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 27/06/2000	Date of completion of this report 05.03.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bretherick, J Telephone No. +49 89 2399 8415 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB99/02018

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-35 as originally filed

Claims, No.:

1-40 as received on 06/02/2001 with letter of 06/02/2001

Drawings, sheets:

1/15-15/15 as originally filed

Sequence listing part of the description, pages:

1-21, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB99/02018

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1,2 5-7,10-40 (partly).

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1,2,5-7, 10-40 (partly) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet
- ☒ the claims, or said claims Nos. 1,2,5-7, 10-40 (partly) are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1,2,5-7,10-40 (partly).
2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/02018

- ☐ restricted the claims.
 - ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1,2,5-7,10-40 (partly), all parts of claims remaining..

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-40
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-40
Industrial applicability (IA)	Yes:	Claims	1-39
	No:	Claims	40, opinion reserved

2. Citations and explanations **see separate sheet**

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB99/02018

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB99/02018

1. The International Examining Authority agrees with the findings of the International Searching Authority that the current application lacks unity within the meaning of R. 13.1 PCT.
 - a. The 2 invention groups are set out according to the following claims.:
 - A. Claims 1-11 and 13-40 partially, claim 12 completely

Polypeptides comprising an unbroken sequence from SEQ ID NO:1 either capable of binding HLA-A2 or of eliciting an immune response from human lymphocytes, nucleic acids coding same and associated products, methods using same, cells pulsed with said protein, diagnostic methods, CTL production methods etc.

[Note that SEQ ID's 43 and 45, derived from SEQ ID NO:2 have been searched with the invention due to their similarity with SEQ ID NOs:42 and 44, respectively].

- B. Claims 1-11, 13-40, all partially.

Polypeptides comprising an unbroken sequence from SEQ ID NO:2, either capable of binding HLA-A2 or of eliciting an immune response from human lymphocytes, nucleic acids coding same expression vectors.. etc...

WO9525530 discloses MAGE-2 derived HLA-A2.1 binding peptides (table III on page 14), methods for their identification and methods to obtain CTL specific for the complex between these peptides and HLA-A2.1. WO9610413 describes methods to type a patient's HLA profile and to identify TRAP-derived peptides which bind said identified HLA. MAGE-8 and MAGE-10 sequences are also disclosed and suggests their use in this method (page 8, lines 36-38; page 15, line 36 - page 16, line 14; pages 47-48, SEQ ID NO: 2, pages 50-51, SEQ ID NO: 22). An immunogenic MAGE-10-derived peptide, as well as the entire MAGE-10 protein, are disclosed in WO9814463 (page 15, lines 10-15; claims 10-11).

In view of the art, the problem is the provision of further members of the MAGE family, which comprise HLA-A2 binding polypeptides. The solutions lie in MAGE-

10 and MAGE-8 and the identification of HLA-A2-binding polypeptide sequences within them.

Since members of the HLA-A2 binding family MAGE are already art, there is no novel common technical feature present common to the solutions presented to the above problem. There is thus a lack of unity of invention under R. 13.1 PCT.

Note that since there was no great additional search effort required, the first invention class also includes SEQ ID NOs: 43 and 45, due to their similarities with SEQ ID NO: 2 and 1.

2. WO99 45954 (published 16/09/1999, filing date 16/03/1999, priority 17/03/1998 , US 09/061,709); WO99 54738 (published 16/09/1999, filing date 13/03/1998), WO 99 61916, published 20/11/1999, filed 28/05/1999, priority 29/05/1998, 60/087,192, are documents citable under **R. 70.10 PCT (Re. Part VI)**.

3. **Regarding Part III:**

Claims 1, 2, 5-7 and 10-40 are directed to a large number of possible polypeptides, their corresponding nucleotide sequences vectors containing same, as well as allied uses and derived products, such as antibodies and the like. The key products, namely the isolated peptides have been defined in terms of having an unbroken amino acid sequence from SEQ ID NO 1 or 2. One further definition is the ability to complex with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A.2.1. In the alternative, the peptide is further defined as having an ability to elicit an immune response from human lymphocytes.

Neither of these subsequent definitions enables the skilled person to identify with any reasonable certainty a candidate molecule, since the subject-matter is defined by a result to be achieved. The subject-matter is thus unclear under Art. 6 PCT and has a scope which is not commensurate with the extent of the disclosure, which is necessarily restricted. The application is therefore also deficient under Art. 5 PCT.

Consequently, a search has only been carried out for subject-matter which is

clear, supported and disclosed in an unambiguous manner. The search has thus been restricted to that subject-matter relating to the nonapeptides of claim 3 and larger peptides containing these sequences, e.g. the decapeptides of claim 9.

As a result, the substantive examination is also to be thus restricted. The claims have been assessed in the light of this. Irrespective of the conclusions regarding unity of invention, R. 13.1 PCT, the remaining claimed subject-matter has not been subject to substantive examination, since this has not been searched (R. 66(1)(e) PCT).

4. Regarding Part V, art. 33 PCT:

- a. US patent 5,686,068 discloses peptide fragments of MAGE-2 which bind specifically to HLA-A2.1 and cause up-regulation of the expression of the corresponding HLA-A2.1 when exposed to 174CEM.T2 cells expressing same. In Table I SEQ ID NO:s 31 and 32 (respectively nona- and decapeptides) as well as the undecapeptide represented by SEQ ID NO: 57 as illustrated in Table II comprise part of the sequences claimed. Although these sequences are not specifically indicated as causing up-regulation of the expression of the corresponding HLA-A2.1, the skilled person would seriously consider an in depth analysis of the sequence 1 or 2 to isolate polypeptides having this function. An inventive step is therefore not accorded to the current subject-matter. The specific peptides cited in, for example claim 4, is considered to be a choice within the illustrated sequence, which has not been demonstrated to have any advantageous or unusual properties over the art polypeptides which might enable an inventive step to be acknowledged. This opinion is reinforced in particular in the light of the specific disclosures of the disclaimer of the peptides of, for example, claim 6.
- b. The information would enable the skilled person to arrive at the claimed subject-matter without the use of inventive skill. This is reinforced by the disclosure of similar sequences derived from MAGE-10 and expressed in vectors (see, *inter alia*: WO 98/14463, in particular Example 10, Example 11; WO92/20356, which advocates the observation of T-cell responses upon stimulation by putative

tumour-rejection antigens; Chen et al. (1998) PNAS Vol. 95. pp. 6919-6923, using cDNA library screening of multiple cancer/testis antigens with allogenic antibody responses).

- c. In Table 1 of Visseren et al. (1997) Int. J. Cancer Vol. 73 pp. 125-130, the peptide described as M2181-189 is also of relevance. The peptide, a derivative of MAGE-2, bound with high affinity to HLA-A*0201 molecules stripped off JY cells (page 126, under "peptide binding assay").
- d. Note that a similar conclusion might be drawn from certain of the other disclosures not currently cited in this opinion.
- e. An opinion as to the industrial applicability under Art. 33(1)(4) PCT of the subject-matter of claim 40 for a method of treating tumours in a patient is reserved, since there are no common and unified criteria within the PCT for such an assessment.

5. Regarding Part VIII; Art. 5 and 6 PCT:

Claims 1, 2 and dependencies 5-7 and 10-40 are formulated in such a manner that the subject-matter is not unambiguously identifiable. This has lead to a limited search (see above). These claims are not clear in scope, thus being deficient under Art. 6 PCT. Moreover, the number of possible peptides of this type (as defined in these claims) is considerable, but the application does not enable the skilled person to find others than those illustrated as concrete examples, the scope of the claimed subject-matter is considered not to be supported by the description to the extent that it does not satisfy the criteria laid out in Art. 5 PCT.

Claims

1. An isolated polypeptide comprising an unbroken sequence of amino acids from SEQ ID. NO. 1, or 2, characterised by an ability to complex with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1.

2. An isolated polypeptide comprising an unbroken sequence of amino acids from SEQ. ID. NO. 1, or 2, characterised by an ability to elicit an immune response from human lymphocytes.

3. An isolated polypeptide as claimed in either one of claims 1 and 2, the polypeptide being a nonapeptide wherein the amino acid adjacent to the N-terminal amino acid is L or M, preferably L, and the C-terminal amino acid is L, V, or I, preferably L.

4. A nonapeptide comprising an unbroken sequence of amino acids from SEQ. ID. NO. 1, or 2, wherein the amino acid adjacent to the N-terminal amino acid is L or M, preferably L, and the C-terminal amino acid is L, V, or I, preferably L, other than a nonapeptide having the amino acid sequence CLGLSYDGL.

5. A nonapeptide as claimed in either of claims 3 and 4, wherein the amino acid in position 3 is Y and/or the amino acid in position 4 is D and/or the amino acid in position 5 is G and/or the amino acid in position 7 is E and/or the amino acid in position 8 is H.

6. A polypeptide as claimed in any one of claims 1-5, other than a nonapeptide having any one of amino acid sequences:-

- (a) FLLFKYQMK;
- (b) FIEGYCTPE; or
- (c) GLEGAQAPL.

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7. A polypeptide as claimed in any one of claims 2-6, further characterised by an ability to complex with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1.
8. A decapeptide comprising a nonapeptide as claimed in any of claims 3-6 and, preferably, an unbroken sequence of amino acids from SEQ. ID. NO. 1, or 2.
9. A nonapeptide having the amino acid sequence GLYDGMEHL or GLYDGREHS, preferably GLYDGMEHL.
10. A decapeptide having the amino acid sequence GLYDGMEHLI or GLYDGREHSV, preferably GLYDGMEHLI.
11. An isolated polypeptide of up to about 93 amino acids in length, characterised by comprising a nonapeptide or a decapeptide as claimed in any of claims 3-10.
12. A polypeptide as claimed in claim 11, comprising of an unbroken sequence of amino acids from SEQ. ID. NO. 1, or 2.
13. A polypeptide as claimed in any of the preceding claims, wherein the unbroken sequence is from SEQ. ID. NO. 1.
14. A polypeptide as claimed in any of the preceding claims and capable of eliciting an immune response from human lymphocytes.
15. A polypeptide as claimed in claim 14 and capable of eliciting an immune response from human lymphocytes when complexed with a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1.
16. A polypeptide as claimed in claim 14 or claim 15, wherein said immune response is an cytolytic response from human T-lymphocytes.

17. An isolated polypeptide or protein comprising a polypeptide as claimed in any of claims 1-16, wherein the amino acid sequence of said isolated polypeptide or protein is not that set out in either of SEQ. ID. NOs. 1 and 2 or that coded for by nucleotides 334-918 of SEQ. ID. NO. 7.

5 18. An isolated polypeptide or protein which is a functionally equivalent homologue to a polypeptide or protein as claimed in any of claims 1-17, wherein the amino acid sequence of said isolated polypeptide or protein is not that set out in either of SEQ. ID. NOs. 1 and 2 or that coded for by nucleotides 334-918 of SEQ.
10 ID. NO. 7.

19. An isolated nucleic acid molecule comprising a nucleotide sequence coding for a polypeptide or protein as claimed in any of claims 1-17, or a complimentary nucleotide sequence, wherein said nucleotide sequence is not that set out in any of
15 SEQ. ID. NOs. 3, 4, 5, 6 or 7.

20. A nucleic acid molecule as claimed in claim 19 and comprising an unbroken sequence of nucleotides from SEQ. ID. NO. 3, 4 or 5, or a complimentary sequence, or an RNA transcript of said nucleic acid molecule.

20 21. A nucleic acid molecule as claimed in claim 19 or claim 20, wherein said nucleotide sequence encodes a plurality of epitopes or a polytope.

22. An expression vector comprising a nucleic acid molecule as claimed in any of
25 claims 19-21 operably linked to a promoter.

23. An expression vector as claimed in claim 22, further comprising a nucleotide sequence coding for a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1, a cytokine or a co-stimulatory molecule, or a bacterial or viral
30 genome or a portion thereof.

24. A host cell transformed or transfected with an expression vector as claimed in claim 22 or claim 23.

25. A host cell as claimed in claim 24, transformed or transfected with an expression vector coding for a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1, a cytokine or a co-stimulatory molecule.

26. A polypeptide-binding agent which selectively binds or is specific for an isolated polypeptide or protein as claimed in any of claims 1-18.

27. A polypeptide-binding agent as claimed in claim 26, comprising an antibody, preferably a monoclonal antibody or an antibody fragment specific for an isolated polypeptide as claimed in any of claims 1-18.

28. A polypeptide-binding agent as claimed in claim 26 or claim 27 which selectively binds or is specific for a complex of a polypeptide as claimed in any of claims 1-18 and a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1, but which does not bind said major histocompatibility molecule alone.

29. A polypeptide-binding agent as claimed in any of claims 26-28, comprising a cytolytic T-cell which is specific for a complex of a polypeptide as claimed in any of claims 1-18 and a major histocompatibility complex molecule type HLA-A2, preferably HLA-A2.1.

30. A polypeptide or protein as claimed in any of claims 1-18, an isolated nucleic acid molecule as claimed in any of claims 19-21, an expression vector as claimed in either of claims 22 or 23, a host cell as claimed in either of claims 24 or 25, or a polypeptide binding agent as claimed in any of claims 26-29, for use in the therapy, prophylaxis or diagnosis of tumours.

31. A pharmaceutical composition for the prophylaxis, therapy or diagnosis of tumours comprising a polypeptide or protein as claimed in any of claims 1-18, a nucleic acid molecule as claimed in any of claims 19-21, an expression vector as claimed in either of claims 22 or 23, a host cell as claimed in either of claims 24 or

25, or a polypeptide binding agent as claimed in any of claims 26-29, optionally in admixture with a pharmaceutically acceptable carrier and optionally further comprising a major histocompatibility molecule type HLA-A2, preferably HLA-A2.1.

5

32. A pharmaceutical composition for the prophylaxis, therapy or diagnosis of tumours comprising a polypeptide or protein as claimed in any of claims 1-18 complexed with a major histocompatibility molecule, HLA, and presented on the surface of an APC, preferably a dendritic cell, wherein said complex is formed by pulsing said APC with polypeptide or protein.

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33. A cell, preferably an APC, and more preferably, a dendritic cell, which has been pulsed with a polypeptide or protein as claimed in any of claims 1-18 to present on its surface said polypeptide or protein as a complex with a major histocompatibility molecule, HLA.

15

34. A pharmaceutical composition as claimed in any of claims 31 and 32 further comprising a co-stimulatory molecule.

20

35. A method of diagnosing disease, preferably cancer, comprising contacting a biological sample isolated from a subject with an agent that is specific for a polypeptide or protein as claimed in any of claims 1-18, or a nucleic acid molecule as claimed in any of claims 19-21 and assaying for interaction between the agent and any of the polypeptide, protein or nucleic acid molecule either free in or forming an integral part of the sample as a determination of the disease.

25

36. A method as claimed in claim 35, wherein the agent is a polypeptide-binding agent as claimed in any of claims 26-29.

30

37. A method of producing a cytolytic T-cell culture reactive against tumour cells, comprising removing a lymphocyte sample from an individual and culturing the lymphocyte sample with a polypeptide or protein as claimed in any of claims 1-

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15, an expression vector as claimed in either of claims 22 or 23, or a host cell as claimed in either of claims 24 or 25.

38. A product comprising cytolytic T-cells reactive against a tumour cell
5 expressing an antigen comprising a polypeptide or protein as claimed in any of claims 1 to 18, for use in the prophylaxis, therapy or diagnosis of tumours.

39. A product as claimed in claim 38 and obtained or obtainable by a method as claimed in claim 37.

10

40. A method of treating tumours in a patient comprising administering a composition as claimed in any of claims 30, 31, 32, 34, 38 or 39 to the patient in an amount effective to control or prevent tumour growth.

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